TISSUE ADHESIVE ARRESTS STROMAL MELTING IN THE HUMAN CORNEA

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The use of cyanoacrylate adhesive in the management of corneal perforation has been well documented.[1] In the present series of cases early use of this topically applied cement has been used effectively to interrupt progressive corneal melting in various ulcerative disorders before anticipated perforation could occur.

SUBJECTS AND METHODS

Proper application of isobutyl 2-cyanoacrylate adhesive requires the magnification provided by the biomicroscope or the operating microscope. Depending on circumstances, the biomicroscope is generally adequate even for young patients (Case 1). Topical anesthetic is required and in some cases an eyelid speculum helps to ensure uninterrupted application and sufficient opportunity for the adhesive film to dry. The ulcer base is debrided with a Weckcel sponge or cotton-tipped applicator, and the circumferential epithelium is removed with a Bard-Parker blade or Kimura spatula to the basement membrane level for a width of at least 1 mm all around. Cultures may be taken from the debrided tissue. The Weckcel sponge ensures a dry field just before the application of cement. Cyanoacrylate adhesive is sparingly applied with the accessory applicator (Fig. 1) to ensure thin but even coverage of the prepared site, because with polymerization the adhesive film thickens somewhat and allowance for this must be made. Attention is paid to total coverage, to complete peripheral application to adjacent normal basement membrane, and to providing as thin a layer as possible so as to minimize discomfort and the tendency of the adhesive plaque to dislodge with eyelid action. When the cement has dried, a thin bandage contact lens (for example, Bausch and Lomb T-series) is placed over the treated cornea. Outpatient follow-up and appropriate adjunctive therapy (for example, antibiotics, collagenase inhibitors, and ascorbate) may be initiated. If the adhesive plaque becomes dislodged prematurely, it can be reapplied. It is beneficial for the cement to remain in place for six to eight weeks to allow

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Fig. 1 (Fogle, Kenyon, and Foster). Cyanoacrylate tissue adhesive with accessory applicator (bottom).

healing. At that time, it can be removed and the bandage lens replaced to guard the surface if a sound epithelium has not regenerated.

The ten cases in this series (Table) represent various types of corneal surface disease, predominantly herpetic keratitis (Cases 1 to 3) and keratitis sicca (Cases 5 and 6), which often precede stromal melting. These conditions responded favorably to early application of cyanoacrylate adhesive with a bandage lens. Adjunctive therapies, such as topical antibiotics, collagenase inhibitors, corticosteroids, medroxyprogesterone acetate, and systemic ascorbate were used; conjunctival transplantation was per formed in one instance (Case 10). Such additional therapies were used only on the basis of individualized indications and careful observation. A favorable response was judged to be a mitigation or frank arrest of the acute melting process, and in all cases relative stability was gained without more invasive emergency measures.

Case Reports

Case 1—A 10-year-old boy developed recurring bilateral keratitis at age 2 years. The condition was diagnosed as stromal herpes. When initially examined in 1974, visual acuity was R.E.: 6/15 (20/50) and

TABLE

Summary of case reports

Case No., Age (yrs), Sex	Disease	Comment
1, 10, M	Herpes simplex	See Case Reports
2, 30, F	Herpes simplex, persistent epithelial defect	Corticosteroid "dependence"; stable after placement of adhesive and soft lens until addition of corticosteroid led to perforation
3, 66, F	Herpes zoster, possible herpes simplex	Melting began after scraping for calcium; stable vascular pannus developed under adhesive and soft lens in place for nine months
4, 40, F	Erythema multiforme (Stevens-Johnson syndrome	See Case Reports
5, 48, F	Rheumatoid arthritis, keratoconjunctivitis sicca	Central ulcer treated and adhesive and lens removed once stable; in one month, required repeat therapy and stabilized quickly
6, 69, F	Keratoconjunctivitis sicca	Medroxyprogesterone and soft lens failed to control central melting; improved in two weeks after adhesive and soft lens application
7, 72, F	Limbal melting in both eyes after cataract surgery	Bilateral application with adjunctive medroxyprogesterone; vascular scarring and intact epithelium developed under adhesive
8, 64, M	Healed perforation after *Pseudomonas* ulcer	Applied twice, promoted vascular scar, allowed keratoplasty later
9, 53, F	Radiation keratitis	Melting arrested at descemetocele
10, 40, M	Alkali burn, history of two penetrating keratoplasties	See Case Reports

Fig. 2 (Fogle, Kenyon, and Foster). Case 1 (herpes simplex). Initial appearance of acute central stromal melting with descemetocele.

L.E.: 6/18 (20/60). There were bilateral stromal opacities and stromal vascularization had occurred in the left eye. Two years later the patient developed an episode of metaherpetic keratitis in the left eye that required patching, hypertonic solutions, idoxuridine, and topical corticosteroids for resolution. This course was repeated seven months later. A year after this second course, a traumatic abrasion in the left eye did not respond to such conservative therapy. It quickly developed into a central descemetocele, suggesting inevitable perforation (Fig. 2). He easily tolerated the application of tissue adhesive at the slit lamp in the manner described previously (Fig. 3). A Bausch and Lomb T-series bandage lens was applied and systemic ascorbate sodium was prescribed. Superficial and deep vessels coursed into the cemented zone, and on removing the adhesive plaque after two months, it was noted that approximately one fourth of stromal thickness had returned. The reapplication of a bandage lens alone, with continued ascorbate sodium therapy, led to near restoration of full corneal thickness within one month. The central leukoma and associated vessels became less conspicuous during the following year, and the resulting visual acuity was 6/9 (20/30) in the treated eye (Fig. 3) .

Case 4—A 40-year-old woman had erythema multiforme of unknown cause in 1963. Marked keratinization of the tarsal conjunctivae developed, with superficial scarring in both eyes, and visual acuity of R.E.: 6/120 (10/200) and L.E.: 6/400 (3/200). No symblephara were present, and the eyes were not dry. Over the subsequent 15 years, 15 surgical procedures were performed, including mucous membrane grafts, conjunctival flaps, superficial keratectomies, lamellar keratoplasties, and four penetrating keratoplasties. The failures of the penetrating keratoplasties were caused by various ocular surface abnormalities, including recurrent erosion, persistent defects, trophic ulcers, and superficial vascularization. However, by using extended-wear soft contact lenses, the patient had visual acuity of R.E.: 6/9 (20/30) and L.E.: 6/12 (20/40) as recorded in July 1977. A year later, visual acuity was R.E.: 6/30 (20/100) and L.E.: 6/18 (20/60), as surface haze and vascularization

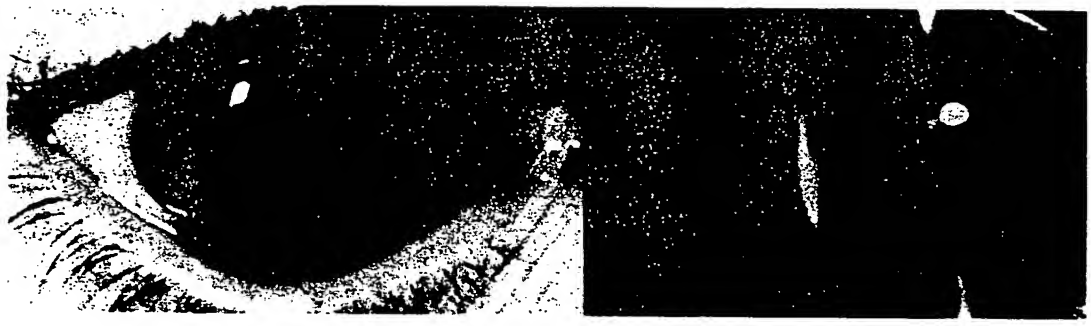

Fig. 3 (Fogle, Kenyon, and Foster). Case 1. Application of adhesive and bandage lens (left) is followed in one year by renewed stromal thickness with minimal scarring and vascularization (right).

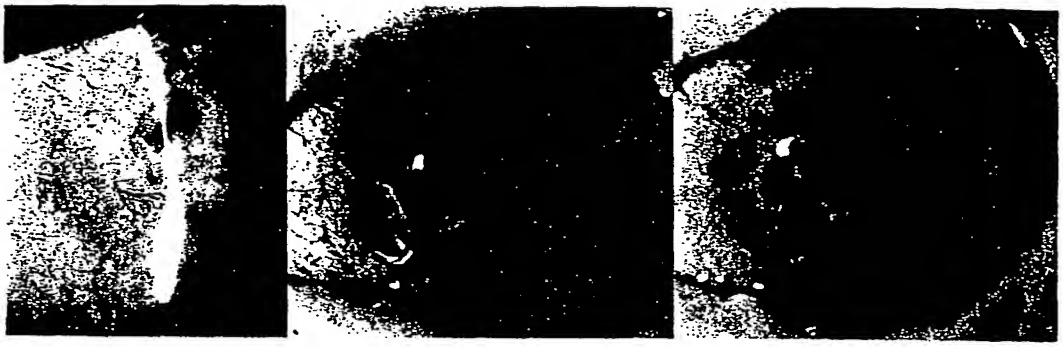

Fig. 4 (Fogle, Kenyon, and Foster). Case 4 (erythema multiforme). Left eye with descemetocele (left) treated with adhesive and a bandage lens (center). After three months, stromal integrity was restored and stabilized (right).

had continued quickly in the left eye. A 5-mm sterile trophic ulcer with 30% stromal melting had developed in the right eye, which was successfully treated with topical antibiotics and acetylcysteine, together with a bandage lens and systemic ascorbate sodium. Two weeks later, a 3-mm defect with 50% stromal melting developed in the left eye, and culture was positive for *Proteus*. The ulcer was managed with antibiotics and adhesive-bandage lens therapy as described previously. Topical corticosteroids were given. Within one week, however, the glue became dislodged, and a pinpoint leak within a descemetocele was observed (Fig. 4). This was managed with tissue adhesive applied under slit-lamp observation, and the patient's cornea gradually vascularized and thickened while he was receiving antibiotics and systemic ascorbate sodium. Two months later, the right eye, still receiving topical corticosteroids, developed a persistent epithelial defect, with stromal melting to a near descemetocele about 5 mm in diameter (Fig. 5). An adhesive-bandage lens was applied and the melting process was arrested. Tear samples were obtained from the melting surface of the right eye and from the quiescent surface of the left eye. The former sample revealed an abundance of polymorphonuclear neutrophils (Fig. 5), whereas the latter contained essentially no inflammatory cells. The cement remained in place on the right eye for four months, after which it dislodged spontaneously to reveal a nearly restored stroma that has remained stable for more than three months.

Case 10—A 40-year-old man received an alkali burn to the left eye in 1968. In 1976 he underwent a trabeculectomy and in 1977 had two keratoplasties in the injured eye. Three months after the second penetrating keratoplasty, a large epithelial defect deteriorated to a 3-mm descemetocele. When initially examined, visual acuity was R.E.: 6/4.5 (20/15) and L.E.: 6/1,200 (1/200). The left cornea showed an opaque, edematous grafted portion with the previ-

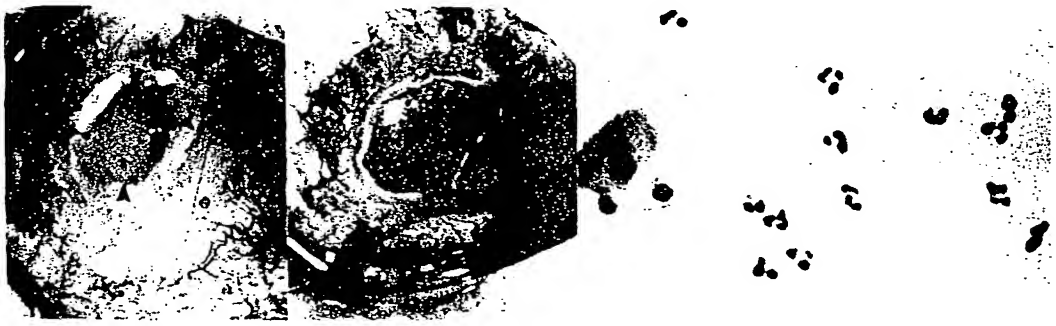

Fig. 5 (Fogle, Kenyon, and Foster). Case 4. Right eye with extensive central descemetocele (arrowheads) (left) treated with adhesive and a bandage lens (center). Tear samples disclosed numerous neutrophils (right) Giemsa, × 1,000).

Fig. 6 (Fogle, Kenyon, and Foster). Case 10 (alkali burn). Central descemetocele (left) with immediate application of adhesive and a bandage lens (center). One week after conjunctival transplantation and adhesive reapplication (right). (Asterisks designate individual grafts of transplanted conjunctiva; arrowheads, tissue adhesive).

ously mentioned central descemetocele (Fig. 6). The anterior chamber appeared deep, and the tactile intraocular pressure was normal. The immediate application of tissue adhesive to the prepared ulcer and adjacent epithelial basement membrane, together with the placement of a bandage lens, was done in the face of imminent perforation. Several days later, a tectonic conjunctival transplant (similar to that recommended by Thoft[2]) was performed. The operation required the careful removal and subsequent replacement of the cement and bandage lens. After four months of healing, the adhesive became dislodged, and a pinpoint leak developed at the center of the incompletely healed descemetocele. Adhesive was then reapplied for a short time (Fig. 7), and subsequently a bandage lens alone was used to promote re-epithelialization. The eye became quiet and comfortable, with an intact surface and medically controlled intraocular pressure.

Bulbar conjunctiva, which was removed during the conjunctival transplant procedure, was examined by light microscopy. Many plasma cells and lymphocytes were noted, but there were few goblet cells (Fig. 8). The keratectomy specimen taken from the area of active corneal melting was also examined, and innumerable acute inflammatory cells, mainly polymorphonuclear neutrophils, were found (Fig. 8).

Discussion

Corneal melting, whatever its setting, is mediated in part by tissue collagenase.[3-11] There is no complete agreement about which cell or cells produce the collagenolytic enzymes, but most evidence has implicated the regenerating

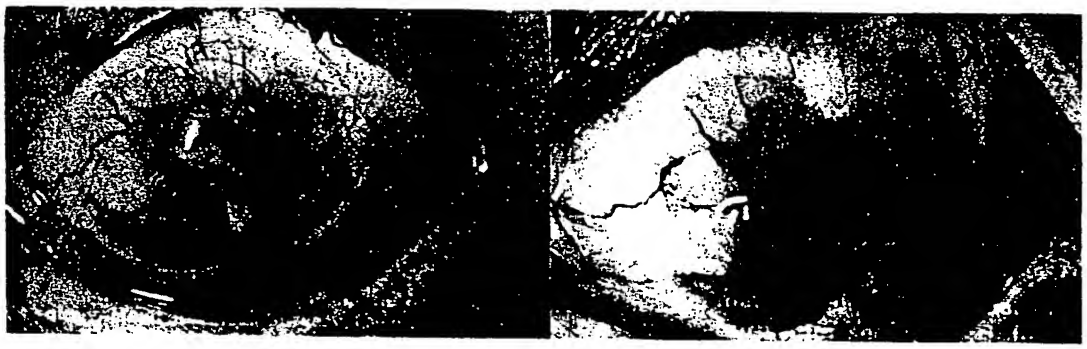

Fig. 7 (Fogle, Kenyon, and Foster). Case 10. A propitious "take" of the conjunctival grafts with adhesive and bandage lens still in place eight weeks postoperatively (left), and eventual resolution of the ulcerated zone with renewed surface five months postoperatively, after removal of adhesive plaque (right).

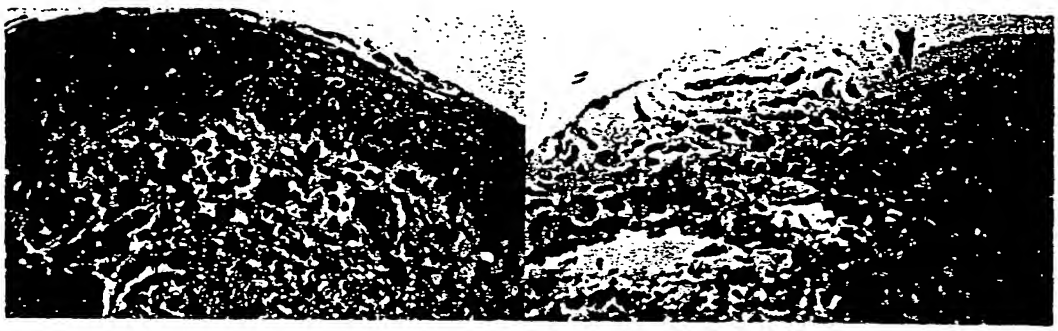

Fig. 8 (Fogle, Kenyon, and Foster). Case 10. Histopathologic section of conjunctival biopsy from nonulcerating region (left) shows absence of goblet cells and stromal infiltration with chronic inflammatory cells, predominantly plasma cells. Section taken from keratectomy material in region of active ulceration (right) discloses numerous polymorphonuclear neutrophils. Note termination of Bowman's layer at arrowhead (phase contrast, paraphenylenediamine, × 450).

epithelium adjacent to an ulcer and its interaction with subjacent keratocytes.[5,7]

Less attention has been directed toward the role of the polymorphonuclear neutrophil in corneal ulceration, despite evidence of potent collagenolytic and proteolytic activity by this inflammatory cell in certain experimental systems.[12-15] Recent experiments and observations have incriminated the polymorphonuclear neutrophil in human and experimental corneal ulcers.

Snip and Kenyon[16] did ultrastructural studies of melting human corneas obtained at keratoplasty for metaherpetic keratitis, stromal herpes, acute homograft reaction, and chemical injury. Stimulated polymorphonuclear neutrophils were present in all actively ulcerating eyes and these cells showed active phagocytosis and degranulation. By contrast, quiet descemetoceles were examined, and the presence of polymorphonuclear neutrophils was negligible.

A decade ago Dohlman and associates[17,18] suggested the "glued-on" contact lens as a plausible means of preventing regenerating epithelium from reaching a zone of damaged and naked stroma, and therefore preventing the presumably critical setting for collagenase production and progressive stromal melting. A recent investigation by Kenyon and associates[19-21] sought to re-evaluate this type of therapy in light of another probable reason for its apparent benefits: the inhibition of stromal infiltration by polymorphonuclear neutrophils. Using alkali-induced corneal melting in the rabbit model, a consistent circumstantial relationship was shown between active polymorphonuclear neutrophils and progressive stromal melting.[20] It was also shown that by removing epithelium from the alkali-burned area and applying a hard contact lens with a complete ring of cyanoacrylate adhesive, the stromal infiltration by polymorphonuclear neutrophils was greatly reduced and melting stopped. This interruption of the melting process was most successful when the contact lens was applied early in the course of melting, before overwhelming numbers of polymorphonuclear neutrophils had accumulated.

These same authors[21] evaluated the problem using direct ulcer coverage with cyanoacrylate adhesive at different stages of stromal melting in thermally damaged rabbit corneas.[19] Here the dried cement

served the same mechanical function as had the more arduously affixed hard contact lens, as melting was either prevented or arrested by direct adhesive application. Morphologic studies showed the ulcerating stromas of control corneas to be quite inflamed, largely with polymorphonuclear neutrophils, whereas corneas with cemented surfaces were essentially accellular in the affected stromal regions. This simpler barrier method of stabilizing stromal ulceration is analogous to our clinical technique.

Various studies suggest that chemotactic factors (such as a serum protease) may recruit polymorphonuclear neutrophils to a site of ulceration.[22,23] In the case of the cornea, this may be from corneoscleral limbus via stroma or from conjunctiva via tear fluid (Fig. 5). Robb and Kuwabara[24] showed the capability of polymorphonuclear neutrophils to arrive at a central corneal ulcer via the tear fluid, after their release from conjunctival vessels. Because polymorphonuclear neutrophils in tears seem to be the first to arrive in such a setting,[22] there may be some interaction between epithelium, keratocytes, or inflammatory cells, in any combination, causing a diffusible chemotactic factor that would elicit a stromal infiltration by limbal polymorphonuclear neutrophils. It is hypothesized that early superficial stromal invasion by acute inflammatory cells from tear fluid serves to start ulceration and to aid in the chemotactic recruitment of added cells via the stromal route. By either mode of access, a "glued-on" contact lens or adhesive application alone, as described in this report, should provide a barrier to both tear fluid and early regenerating epithelium and, thus, deter the invasion of stroma by polymorphonuclear neutrophils and prevent the accompanying damage.

Many investigators have sought to develop a reliable chemical or pharmacologic treatment that would prevent or combat the production or effect of collagenolytic enzymes in melting corneas as shown by published reports on acetylcysteine,[4,5] ascorbate,[25-27] ethylenediaminetetraacetic acid,[11] and medroxyprogesterone.[28] Although each of these agents has been shown to limit corneal melting in at least the experimental situation, there is still no dependable means of preventing progressive melting and perforation in an array of clinical settings. It is for this reason that the clinical technique described in this report was derived from the clinical and laboratory work of recent years, which implied a significant role for the polymorphonuclear neutrophil in stromal matrix degradation. In addition to the barrier effect described previously, a certain amount of structural support is undoubtedly given by the cement film, especially if care is taken to apply it fully to exposed circumferential basement membrane. If indicated, adjunctive therapies may be continued or initiated.

In an extremely torrid and widespread inflammatory ulceration, as may occur in Mooren's ulcer[29] or Wegener's granulomatosis, in all likelihood a preemptive accumulation of polymorphonuclear neutrophils, proteases, and collagenase may render adhesive application untimely and ineffective. However, in circumscribed corneal ulcerations that threaten to melt progressively and perforate, we suggest that the early application of tissue adhesive, in the simple manner described, may help to deter the course to perforation until reparative processes can stabilize the compromised cornea.

Summary

The direct early application of cyanoacrylate adhesive to a prepared ulcer bed and adjacent basement membrane, followed by placement of a bandage lens, gave good results in ten patients with corneal ulceration. The patients had ulceration with keratitis sicca, herpes

keratitis, and other surface diseases. Progressive melting was arrested in all cases, and concurrent adjunctive therapies were used as indicated. The technique is quick and simple.

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